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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
PAPPU, SITA S

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/24/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,902	ABINA, AMINE	
	Examiner	Art Unit	
	Sita Pappu	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *17,18,23-29,31-42 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,19-22,27,29,30 and 43-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

IDS filed in paper # 7 on 02/14/2002 has been entered. Currently, claims 1-48 are pending in the instant application. This Office Action is in response to the communication filed by the Applicant in paper # 9, on 03/06/2002.

Election/Restrictions

Applicant's election, with traverse, of Group I, claims 1-16, 19-22, 27, 29-30, and 43-47, is acknowledged. Applicant's election of viruses, recited in claim 2, as the species for search purposes is acknowledged. Applicant traversed on the grounds that there is no undue burden on the Examiner to examine Groups I and II concurrently. Applicant's arguments are fully considered but are not found persuasive. Group I is directed to gene therapy by administering a nucleic acid while Group II encompasses protein therapy. Thus, these are distinct Groups and are not rejoined. This restriction requirement is still deemed proper and is made FINAL.

Accordingly, claims 17, 18, 23-26, 28, 31-42 and 48 are withdrawn from consideration as being directed to non-elected invention.

This paper contains an examination of the claims 1-16, 19-22, 27, 29-30, and 43-47 on their merits. Claims 1-16, 19-22, 27, 29-30, and 43-47 of Group II, encompass protein administration but the elected invention is limited to the administration of a nucleic acid. Thus, the claims continue to encompass non-elected subject matter. Claims 1-16, 19-22, 27, 29-30, and 43-47 are examined only to the extent they encompass the elected subject matter.

Priority

Applicant's priority to the filing date of 08/03/2001 is acknowledged.

Drawings

Drawings are approved by the draftsperson.

Claim Objections

Claims 5, 11, 14-16, 19-22, 43-45 are objected to under 37 CFR 1.75(c) as being in improper form. See MPEP § 608.01(n).

Claim 5 recites "method according to claims 1 to 4". Use of claim language such as "method according to any one of claims 1 to 4" is suggested. Claims 19-22 are objected to insofar as they depend from claim 5.

Claim 11 recites "method according to claims 1 to 10". Use of claim language such as "method according to any one of claims 1 to 10" is suggested. Claims 19-22 are objected to insofar as they depend from claim 11.

Claim 14 recites "method according to claims 12 to 13". Use of claim language such as "method according to any one of claims 12 to 13" is suggested. Claims 15-16 are objected to insofar as they depend from claim 14. Claims 19-22 are objected to insofar as they depend from claims 14.

Claim 16 recites "method according to claims 14 and 15". Use of claim language such as "method according to any one of claims 14 and 15" is suggested. Claims 19-22 are objected to insofar as they depend from claim 16.

Claims 19, 21 recite "method of claims 1-16". Use of claim language such as "method according to any one of claims 1 to 16" is suggested. Claims 20-22 are

objected to insofar as they depend from claim 19. Claim 22 is objected to insofar as it depends from claims 20 and 21.

Claim 22 recites "method according to claims 20 and 21". Use of claim language such as "method according to any one of claims 20 and 21" is suggested.

Claim 43 recites "method according to claims 1 to 26 and 33, use of a method according to claim 27 to 32". A claim cannot depend from more than one set of claims. Use of claim language such as "method according to any one of claims 1-16, 19-22, 27, 29, 30" is suggested. Claims 44 and 45 are objected to insofar as they depend from claim 43.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27, 43-45 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). Claims 43-45 are rejected insofar as they depend from claim 27.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 19-22, 27, 29-30, and 43-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention and the breadth of claims:

The nature of the invention is directed toward using the method of inhibiting the formation of neutralizing antibodies to enhance sustained and long term expression of exogenous nucleic acids in gene therapy of a mammal in treating a variety of diseases. No other use for the method of inhibiting the formation of neutralizing antibodies is asserted in the specification.

Claims 1-16, 19-22, 27, 29-30, and 43-47 are directed to a method of inhibiting in a mammal, including human, formation of neutralizing antibodies directed against a heterologous protein by coadministering an agent in an amount sufficient to deplete or

inhibit the antigen presenting cells of said mammal and a nucleic acid sequence encoding a heterologous protein, wherein the agent is an adenovirus and the heterologous protein encoding sequence is operably linked to a promoter that directs the expression of the gene in the antigen presenting cells of the mammal.

The claims encompass the use of the method in any mammal, and thereby cover all organisms including human beings. The claims encompass gene therapy, because the purpose of the inhibition of neutralizing antibodies is for the sustained expression of an exogenous nucleic acid, which, as disclosed by the specification, is for therapeutic purposes in the treatment of a variety of diseases. The claims encompass inhibiting the neutralizing antibodies directed to any and all heterologous proteins involved in the etiology of any and all diseases claimed. Thus, the claims have a very broad scope.

State of the art:

At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the

rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Further, in a review of genetic immunization, Ertl and Zhiang emphasize the critical role of the antigen by stating that, " although any antigens can be delivered

by genetic immunization, some proteins upon expression by plasmid vectors remain immunologically silent. The principles that govern success versus failure of genetic immunization with regard to each individual protein remain to be elucidated" (Ertl et al. (1996), Viral Immunology, Vol. 9 (1), page 2, lines 32-35).

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Amount of Direction provided and existence of working examples:

The prior art teaches the unpredictability of achieving therapeutic levels of gene expression using the methods and constructs available at the time of filing. In cases where prior art does not teach how to use the method, all the guidance for practicing the invention must come from the specification.

The specification discloses a single example of using the method of the invention in a mouse injected with an adenoviral vector carrying human thrombopoietin (huTPO), wherein the said mouse exhibited a functional knockout phenotype for the endogenous mouse TPO (bridging paragraph, pages 23 and 24). The KO phenotype according to the disclosure is induced by the cross-reactive antibodies against TPO following injection with huTPO construct. Further, specification (page 23, line 11) discloses that when adenoviruses are administered to a mammal in an amount greater than that required to trigger an immune response, are able to locally saturate or inactivate the antigen-presenting cells (APCs), leading to tolerance to a compound such as a protein subsequently administered to a mammal. However, specification also discloses that this

result varies from on experiment to the other i.e., from one virus stock to another (page 24, line 4) and that there is a need to determine the exact dose for induction of functional inactivation (page 25, line 13). The specification does not teach any other instances where the method of the instant invention would successfully generate a functional knockout such that a skilled artisan would accept the use of this method in generating a KO of any gene in any mammal. Further, the method of the instant invention would require undue experimentation to gather the knowledge on the availability of the heterologous genes, the temporal expression patterns of the endogenous genes as well as their levels of expression and regulation mechanisms and determining the appropriate tolerigenic and/or immunogenic doses such that a skilled artisan would be able to use the appropriate dose to generate a KO of any gene in any mammal. Further, the specification discloses that the KO mouse generated was fortuitous (page 23, line 30) leading one of skill to believe that this result is unpredictable and is not reproducible. In such an instance, the specification should provide sufficient guidance on how one can generate a KO of any gene in any mammal using the method of the instant invention.

Although the specification discloses the object of the instant invention is to overcome the problems of host immune response and the difficulty of achieving sustained levels of gene expression with a therapeutic effect in gene therapy, the disclosed example does not provide enough guidance on how this objective is achieved such that a skilled artisan can use the method of the instant invention in a method of

treating any and all the diseases in any and all the mammals claimed using any and all of the heterologous gene products in an adenoviral vector construct.

The specification does not teach the different proteins involved in producing the different etiologies associated with any of the diseases claimed and what levels of immune responses are generated in the therapy of any of these diseases using any heterologous gene constructs and what tolerigenic dose (TD) and immunogenic doses (ID) are required to generate tolerance against gene therapy using any of the heterologous gene constructs using adenoviral vectors in any mammal. This aspect is particularly relevant since the disclosure teaches that the results vary from one virus stock to another. Further, the specification fails to disclose whether the modulating effect seen in mouse is long enough to see a therapeutic effect and how this effect would correlate to expectations of therapeutic effects in any and all mammals and how this method can be extrapolated to all the mammals, such that one of skill in the art would accept that their method would result in a therapeutic outcome and be able to practice the method using the guidance provided in the specification.

The specification does not provide guidance to overcome the art recognized unpredictabilities of gene therapy because it lacks correlative evidence between the the method of the invention which in the instant case resulted in a functional knockout and its usefulness in achieving a therapeutic effect against all the diseases claimed in all the mammals. It would require undue experimentation on the part of a skilled artisan to determine the vector, the dosage, frequency and route of administration, to obtain a level of expression that would result in a therapeutic effect, while at the same time

achieving neutralization of the antibodies and the corresponding immune response in all the mammals using any gene of interest.

Predictability of the Art, Amount of Experimentation and Skill level of the artisan:

While it is relatively routine in the gene transfer art to achieve expression at non therapeutic levels, i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Thus, when there is deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, the Applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of expression of a DNA product in an art recognized animal model or patient as claimed.

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention as specified and use the invention as claimed. The specification and the working examples do not provide sufficient guidance to practice the invention as claimed. Therefore, in the absence of specific guidance and working examples, the use of the claimed method is unpredictable. In such a situation, one skilled in the art would not know how to use the invention as claimed, without undue experimentation. In view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to use the invention.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids, the lack of guidance provided by the specification, the lack of guidance concerning the treatment of various diseases using the claimed method of the instant invention, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in using the claimed method for the purpose disclosed in the specification. Thus the specification does not enable one skilled in the art to use the claimed invention over any scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 19-22, 27, 29, 30, 43-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11, 27, 43-47 are indefinite in that they are directed to a non-elected invention. Claims 1, 6, 7, 27 and 43-47 recite the administration of heterologous protein and as such the metes and bounds of the claims are not clearly set forth. Claims 2-5, 8-11 are objected to insofar as they depend from claims 1, 6 or 7. Applicant is required to amend the claims 1, 6, 7, 27 and 43-47 such that they are drawn only to the elected invention.

Claims 27, 29, 30, 43, 46, 47 are indefinite in that they are directed to a non-elected invention. Claims 27 and 29 depend from claim 23, which is directed to a non-

elected invention and as such the metes and bounds of the claims are not clearly set forth. Claim 43 depends from non-elected claims 17, 18, 23-26, 28, 31-33. Claims 46 and 47 depend from non-elected claims 17, 18, 23-26, 33. Applicant is required to amend claims 27, 29, 43, 46, 47 such that they are drawn only to the elected invention. Claim 30 is objected to insofar as it depends from claim 29. Claims 44, 45 are objected to insofar as they depend from claim 43.

Claims 4 and 13 are indefinite in its recitation of "a fragment thereof". It is not clear how a fragment of a virus can be selected. Claims 14-16 are rejected insofar as they depend from claim 13. Claims 19-22 are rejected insofar as they depend from claims 4 and 13.

Claim 6 is indefinite in its recitation of "administered prior said heterologous protein". Use of claim language such as "administered prior to said heterologous protein" is suggested. Claims 19-22 are rejected insofar as they depend from claim 6.

Claims 8, 12 are indefinite in their recitation of "the genome of which comprising". Use of claim language such as "the genome of which comprises" is suggested. Claims 9-11 are rejected insofar as they depend from claim 8. Claims 13-16 are rejected insofar as they depend from claim 12. Claims 19-22 are rejected insofar as they depend from claims 8 and 12.

Claims 9, 10, 12 are indefinite in its recitation of "regulation sequences". Use of claim language such as "regulatory sequences" is suggested. Claim 11 is rejected insofar as it depends from claims 9 and 10. Claims 13-16 are rejected insofar as they

depend from claim 12. Claims 19-22 are rejected insofar as they depend from claims 9, 10 and 12.

Claim 13 is indefinite in its recitation of "the genome of which not expressing". Use of claim language such as "the genome of which is not expressing" is suggested. Claims 14-16 are rejected insofar as they depend from claim 13. Claims 19-22 are rejected insofar as they depend from claims 13.

Claim 20 is indefinite in its recitation of "associated syndromes thereof". It is not clear what the claim is referring to. Claim 22 is rejected insofar as it depends from claim 20.

Claims 21, 29 are indefinite in their recitation of "the therapy". There is no antecedent basis for this phrase in the claims. Claim 22 is rejected insofar as it depends from claim 21. Claim 30 is rejected insofar as it depends from claim 29.

Claim 27 provides for the use of a method according to claim 23 of inhibiting in a mammal formation of neutralizing antibodies, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

There is no antecedent basis in claim 27 for "said agent" and "step (ii)". Claim 27 is indefinite in its recitation of "an amount equal or greater than". Use of claim language such as "an amount equal to or greater than" is suggested. Claims 43-45 are rejected insofar as they depend from claim 27.

Claim 29 is indefinite in its recitation of "ethiology". Use of claim language such as "etiology" is suggested.

Claim 30, 46, 47 are indefinite in their recitation of "chosen among". Use of claim language such as "selected from the group consisting of" is suggested.

Claim 30 is indefinite in its recitation of "parasites infections, funguses infections". Use of claim language such as "parasitic infections and fungal infections" is suggested.

Claim 43, and 45 are indefinite in their recitation of "selected among". Use of claim language such as "selected from the group consisting of" is suggested. Claim 44 is rejected insofar as it depends from claim 43.

Claim 44 is indefinite in its recitation of "chosen among". Use of claim language such as "selected from the group consisting of" is suggested. Claim 45 is rejected insofar as it depends from claim 44.

Claim 47 is indefinite in its recitation of "intradermic injection,". Replacing the "," with a "." Is suggested.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone

numbers for the organization where this application or proceeding is assigned are (703) 308 4242 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
April 19, 2002